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COVID-19 Pozitif Gebelerin Hastaneye İlk Başvurularındaki Demografik, Klinik ve Laboratuvar Verilerinin Değerlendirilmesi

Evaluation of Demographic, Clinic and Laboratory data of COVID-19 (+) Pregnants in their First Admission to Hospital

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ÖZ

Amaç: Acil Servise başvuran gebelerin demografik, klinik ve laboratuvar verilerini değerlendirilerek, gebeliğin farklı trimesterlerinde COVID-19 hastalığının klinik seyrini araştırmak.**Gereç ve Yöntemler:** Olgular semptomlara ve oksijen saturasyon (Sat O2) değerine göre asemptomatik, hafif semptomatik ve şiddetli hastalık olarak 3 grupta incelendi. Laboratuvar testlerinde lenfopeni, yüksek CRP, ferritin ve D-dimer seviyeleri kötü prognostik faktörler olarak kabul edildi.**Bulgular:** COVID-19'lu 678 gebenin 118'i (%17.4) birinci trimesterde, 261'i (%38.5) ikinci trimesterde ve 299'u (%44.1) üçüncü trimesterdeydi. 120'si sadece COVID-19 enfeksiyonuna bağlı olmak üzere toplam 257 (%37,9) COVID-19 (+) gebe hastaneye yatırıldı. Olguların 57'sinde (%8.4) ağır hastalık saptandı, bunların 29'u (%50.9) 2. trimesterde, 26'sı (%45.6) 3. trimesterdeydi. Ağır hastalık insidansı gebeliğin sonraki haftalarında ilk trimestere göre anlamlı derecede yüksekti ($p=0.004$). Kötü prognostik laboratuvar kriterlerinin trimesterlere göre dağılımı incelendiğinde, COVID-19'lu gebelerin %22,9'u ilk trimesterde en az 1 kötü prognostik laboratuvar kriterine sahipken, bu oran ikinci ve üçüncü trimesterlerde sırasıyla %41,7 ve %63 idi ($p<0.001$).**Sonuç:** Bu çalışmada, COVID-19 pozitif gebelerde hastalığın seyrinin gebeliğin ileri haftalarında ilk trimestere göre daha şiddetli olduğunu gözlemledik.**Anahtar Kelimeler:** COVID-19, gebelik, trimester

ABSTRACT

Aim: To investigate the clinical course of COVID-19 in different trimesters of pregnancy by evaluating the demographic, clinical and laboratory data of pregnant women who applied to the Emergency Service.**Materials and method:** Cases were examined in 3 groups as asymptomatic, mild symptomatic and severe disease according to symptoms and oxygen saturation (Sat O2). High levels of CRP, ferritin, D-dimer and lymphopenia in blood tests were considered as poor prognostic factors.**Results:** Of 678 pregnant women with COVID-19, 118 (17.4%) were in the first trimester, 261 (38.5%) were in the second trimester and 299 (44.1%) were in the third trimester. A total of 257 (37.9%) COVID-19 (+) pregnant women were hospitalized and 120 of them were due to COVID-19 infection without any obstetric indications. Severe disease was detected in 57 (8.4%) of the cases; 29 of them (50.9%) in the 2nd trimester and 26 (45.6%) in the 3rd trimester. The incidence of severe disease was significantly higher in the later weeks of pregnancy compared to the first trimester ($p=0.004$). When the distribution of the poor prognostic laboratory criteria according to trimesters was examined, 22.9% of pregnant women with COVID-19 had at least one poor prognostic laboratory criterion in the first trimester, while this rate was 41.7% and 63.9% in the second and third trimesters, respectively ($p<0.001$).**Conclusion:** In this study, we observed that the course of the disease in COVID-19 positive pregnant women was more severe in the later weeks of pregnancy compared to the first trimester.**Key Words:** COVID-19, pregnancy, trimester**Sorumlu Yazar/ Corresponding Author:** Özlem GÜNDÜZ**Adres:** Ankara Şehir Hastanesi Kadın Doğum Hastanesi, Bilkent, Ankara, Türkiye.**E-mail:** dr.ozlem-yasar@hotmail.com

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INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to an unprecedented global health crisis. While many infected people are asymptomatic or have mild symptoms, some develop serious disease that can lead to pneumonia, acute respiratory distress syndrome, multisystemic dysfunction, and death. The virus appears to be more dangerous in some high-risk individuals, especially the elderly or those affected by multiple diseases (1). Pregnant women are a particularly vulnerable group to critical illnesses related to COVID-19 due to immunologic, physiological, and anatomical changes during pregnancy (2). Since the onset of the pandemic, many systematic reviews and large observational cohorts have reported a higher risk of severe disease in pregnant women (3). In addition, it was observed that the risk of serious illness and need for intensive care unit were highest in pregnant women in the third trimester (4).

In this study, we aimed to compare the clinical course of COVID-19 in the first, second, and third trimesters of pregnancy by evaluating the data of infected pregnant women who applied to the emergency department of one of the main national pandemic centers.

MATERIAL AND METHODS

This cross-sectional survey study was conducted on 678 pregnant women who were diagnosed with COVID-19 by RT-PCR analysis between October 1, 2020 and May 1, 2021 in Ankara City Hospital. Demographic features, clinical signs and laboratory test results were obtained from hospital records. The study protocol was approved by both the Institutional Ethics Committee (E2-21-581) and the Turkish Ministry of Health.

Vital signs were checked (heart rate, rhythm, respiratory rate, blood pressure, body temperature and Sat O₂) and obstetric evaluation was performed after taking the history of each patient. Then thorough physical examination was done by an infectious disease specialist. Basic laboratory tests including complete blood count, C-reactive protein (CRP), procalcitonin, clinical biochemistry parameters, cardiac enzymes, coagulation parameters, fibrinogen, D-dimer, ferritin were carried out. Chest X-ray and chest CT examination were not performed on any of the pregnant women.

Cases were divided into 3 groups as asymptomatic, mild symptomatic (uncomplicated) and severe disease according to the definitions in the national COVID-19 guideline (https://covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf?type=file) (Table 1).

Table 1: Definitions of COVID-19 disease severity according to the national COVID-19 guide

Mild symptomatic (=uncomplicated)	Fever and/or muscle/joint pain and/or cough and/or sore throat are present, BUT No respiratory distress (no dyspnea, respiratory rate <24/min and SatO ₂ >93% in room air)
Severe Disease	Fever and/or muscle/joint pain and/or cough and/or sore throat are present AND Respiratory distress present (dyspnea or air hunger and/or respiratory rate >24/min and/or SatO ₂ <93%)

As defined in the national COVID-19 guide, poor prognostic factors in blood tests (lymphocyte count<800 mg/ml, ferritin>500ng/ml, D-Dimer>1700ng/ml, CRP greater than 10 times the upper limit of normal value) are indicative of severe disease. In this study, we investigated the correlation between poor prognostic factors and disease severity.

Statistical analysis

Statistical analyses were performed by using SPSS (version 21.0; IBM Corporation, NY, USA). Descriptive data were expressed as number (n) and percentage (%), mean \pm SD, median (minimum - maximum). Chi-square test was used for intergroup comparisons of categorical data. p-values \leq 0.05 were considered statistically significant.

RESULTS

In total, 257 (37.9%) of 678 COVID-19 (+) pregnant women were hospitalized; 137 for obstetric reasons, and 120 only for COVID-19 infection. Despite being asymptomatic, 28 were hospitalized because of mutant virus detection, 24 with poor laboratory prognostic factors and 11 for social reasons. The number of patients with severe disease at admission was 57.

The number of asymptomatic pregnant women was 284 (41.9%). At least one symptom was present in 394 (58.1%) cases (Table 2). Oxygen saturation (SatO₂) in room air was found to be below 90% in 10 (1.5%) and between 90-93% in 47 (6.9%) pregnant women. In 91.6% of cases, SatO₂ was \geq 94%.

Severe disease was present in 57 (8.4%) cases; 29 (50.9%) of them were in the 2nd trimester and 26 (45.6%) were in the 3rd trimester. It was observed that the rate of severe disease was statistically significantly higher in the advanced weeks of gestation than in the first trimester ($p=0.004$).

Table 2: Symptoms of COVID-19 positive pregnant patients

Symptoms	
Cough	n=172 (25.4%)
Dyspnea	n=94 (13.9%)
Myalgia/artralgia	n=64 (9.4%)
Taste/smell loss	n=60 (8.8%)
Headache	n=59 (8.7%)
Fever (>38)	n=54 (8.0%)
Fatigue	n =50 (7.4%)
Sore throat	n =43 (6.3%)
Flu like symptoms	n =21 (3.1%)
Low back/back pain	n =13 (1.9%)
Diarrhea	n =12 (1.8%)

In laboratory findings lymphocyte count was <800 mg/dl in 123 patients, D-Dimer level was >1700 ng/ml in 205 patients, ferritin level was >500 ng/ml in 35 patients, CRP value more than 10 times the upper limit in 76 patients.

At least one poor prognostic criterion was found in 48.2% (n=327) of cases. When the distribution of the presence of poor prognostic laboratory criteria according to trimesters was examined, 22.9% of the patients with COVID-19 had at least one poor prognostic laboratory criterion in the first trimester, while this rate was 41.7% and 63.9% in the second and third trimesters, respectively ($p<0.001$) (Table 3).

Table 3: Presence of poor prognostic factors in laboratory tests in pregnant women with COVID-19 (+) according to their gestational age

	I.Trimester (n=118) %17.4	II.Trimester (n=261) %38.5	III.Trimester (n=299) %44.1	P
Asymptomatic (n=284)	52 (25.5%)	53 (26%)	179 (48.5%)	
Mild symptomatic (n=337)	64 (19%)	179 (53.1%)	94 (27.9%)	
Severe illness (n=57)	2 (3,5%)	29 (50.9%)	26 (45.6%)	
Rate of severe illness	1,6%	11.1%	8.7%	($p=0.004$).
Rate of the patients had at least one poor prognostic laboratory finding (n=327)	22.9% (27/118)	41.7% (109/261)	63.9% (191/305)	($p<0.001$)
Intensive Care Unit (n=12)	1	5	6	
Mechanical Ventilation (n=6)	1	1	4	
Mortality (n=4)	1	1	2	

Among 12 critically ill pregnant women who required admission to the intensive care during hospitalization, only 1 was in 1st trimester, 5 were in 2nd trimester and 6 were in 3rd trimester. Six patients were intubated in intensive care unit (ICU); one patient was in first trimester, one patient was in second trimester and four patients were in third trimester. Maternal mortality was observed in 4 (0.59%) cases. As shown in Table 3, we observed that in the 2nd and 3rd trimesters, especially in the 3rd trimester, the severity of the disease and the possibility of having poor prognostic laboratory findings were significantly higher than the first trimester.

DISCUSSION

Pregnant women are more susceptible to develop severe illness after respiratory viral infection due to physiological changes of the immune and cardiopulmonary systems during pregnancy (5). During the 2009 pandemic outbreak, 5% of all Influenza A subtype H1N1-related deaths belonged to pregnant women (8). Also both SARS-CoV and MERS-CoV have been associated with higher case fatality rates and more severe complications during pregnancy (6, 7). Compared with SARS and MERS, COVID-19 appears to be less lethal and most of the pregnant women with COVID-19 in literature were asymptomatic or only had mild symptoms (7). However, as noted in many reports, special attention should be paid to this vulnerable group, as pregnant women are at higher risk of hospitalization and admission to the ICU compared to non-pregnant women (8, 9).

In the vast majority of cases, the course of COVID-19 during pregnancy had been reported as asymptomatic (10). The symptomatology was similar with other populations and also no

specific pregnancy-related COVID-19 symptoms were known (11). In our study 284 (41.9%) of cases were asymptomatic and 394 (58.1%) cases were symptomatic. We observed mild symptoms in 337 (49.7%) symptomatic patients and respiratory distress in 57 (8.4%) patients. Among severely symptomatic women, 12 (1.76%) were critical and admitted to ICU. Six (0.73%) patients required invasive mechanical ventilation and maternal mortality was 4 (%0.58).

The observed rates of disease severity and mortality is in line with recent analyses in literature. Delahoy et al. reported that 54.5% of 598 pregnant women with COVID-19 were asymptomatic and 45% symptomatic at admission. Of these, 7.3% required an ICU, 3.8% were intubated and 0.33% died (12). According to the findings of a recent systematic review, 6 % of 367 pregnant patients developed severe pneumonia, 2.8% required mechanical ventilation and maternal mortality was 0.54% (13). It was reported in another study that 14 of 43 (32.6 %) COVID-19 (+) pregnant women had no symptom at the time of admission to hospital. Of 29 (67.4%) symptomatic patients, 86% were mild, 9.3% were severe and 4.7% were critical (14). Similar results were found in our study, with 85.6% mild, 11.4% severe and 3% critical of 394 (58.1%) symptomatic patients.

Mullins et al. evaluated the outcomes of 4,005 pregnant women with SARS-CoV-2 infection using data from the 2020 UK PAN-COVID study and the US AAP-SONPM National Perinatal COVID-19 registries and reported the maternal mortality rate of 0.2–0.5% (15).

Studies during the COVID-19 pandemic have shown that the vast majority of cases occur in the third trimester of pregnancy (16-19). Also in this study, 18.6% (n=126) of COVID-19 (+) pregnant women were in the 1st trimester, 36.4% (n=247) were in the 2nd trimester and 45.0% (n=305) were in the 3rd trimester.

Of 57 cases with severe disease, 29 (50.9%) were in the 2nd trimester and 26 (45.6%) were in the 3rd trimester. When the severity of the disease was examined according to trimesters, it was observed that the rate of severe disease was higher in the advanced weeks of gestation than in the first trimester ($p=0.004$). This finding is in line with previous studies on pregnant women with COVID-19 (4, 20, 21).

When we analyzed the literature on the immunology of SARS-CoV-2 infection, pregnant women had lymphopenia, elevated C-reactive protein and D-dimer levels and an altered immune response that predisposed them to severe or critical COVID-19 (22, 23). In this study these laboratory findings are accepted as poor prognostic factors according to the guidance of the National COVID-19 guideline.

At least one poor prognostic criterion was found in 327 (48.2%) cases. When the distribution of the presence of poor prognostic laboratory criteria according to trimesters was examined, 22.9% of the patients had at least one poor prognostic laboratory criterion in the first trimester, while this rate was 41.7% and 63.9% in the second and third trimesters, respectively ($p<0.001$).

Due to the significant physiological changes that occur in the respiratory system and altered cell mediated immunity during pregnancy, susceptibility to respiratory pathogens and the risk of complications of respiratory tract infectious increa-

se (24, 25). With the enlargement of the uterus and the structural changes of the ribcage, the diaphragm is elevated, chest wall compliance is decreased, the functional residual capacity (FRC) and expiratory reserve volume (ERV) are reduced. A decrease in FRC with an increase in oxygen consumption lowers the mother's oxygen reserve (26). These physiologic changes including congestion and increased secretions, reduce the tolerance to hypoxia and lead to physiological dyspnea as well as increased susceptibility to respiratory pathogens. The greatest changes occur in advanced weeks of pregnancy and majority of pregnant women complain about breathlessness in the third trimester. In addition to physiological dyspnea; shortness of breath due to pneumonia in COVID-19 can increase the risk of hypoxemia and exacerbate the clinical presentation (27). Especially in the third trimester, significant fluid exchanges between interstitial, intracellular and intravascular compartments, maximum maternal cardiac output, catecholamine fluctuation and release of inflammatory mediators may put the patient at risk of endothelial dysfunction, pulmonary edema, myocardial edema and cardiac dysfunction (28).

Also, the physiological hypercoagulation state, which occurs when coagulation factors such as fibrinogen and D-dimer rise above the initial value of 50% in the third trimester, increases the risk of coagulation disorders seen in COVID-19 (29).

CONCLUSION

This study on pregnant women with COVID-19 found a significant relationship between the severity of the disease and the trimester of pregnancy. The incidence of severe disease and poor prognostic laboratory findings in advanced weeks of gestation was significantly higher than in the first trimester. In early pregnancies with COVID-19, the disease has a milder course in terms of both clinical and laboratory findings.

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